

Research article

First-Line Pembrolizumab Therapy of Non-Small Cell Lung Cancer: Baseline Metabolic Biomarkers Predict Outcomes

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Simple summary

Positron-emission tomography/computed tomography (PET/CT) is used for staging of non-small cell lung cancer (NSCLC) and can help to estimate prognosis in patients treated with immune checkpoint inhibitor (ICI) therapy. Most available data in that field were derived from cohorts treated in higher therapy lines using ICI monotherapy with different drugs. Currently however, most advanced NSCLC patients receive ICI monotherapy or a combination together with cytotoxic chemotherapy already as first-line treatment. We evaluated predictive PET/CT biomarkers in 85 patients receiving first-line ICI, 70 (82%) of them as chemotherapy-ICI combination. We found that patients with a higher metabolically active tumor volume (MTV) had a significantly poorer survival and lower radiological response rate. In patients with high MTV, a concomitantly low bone marrow to liver ratio indicated a better prognosis. Our results demonstrate that PET/CT-derived biomarkers can aid therapeutic decision-making in ICI-treated NSCLC.

Abstract

Quantitative biomarkers derived from positron-emission tomography/computed tomography (PET/CT) have been suggested as prognostic variables in immune-checkpoint inhibitor (ICI) treated non-small cell lung cancer (NSCLC). As such data for first-line ICI therapy and especially for chemotherapy-ICI combinations are still scarce, we retrospectively evaluated baseline ^{18}F -FDG-PET/CT of 85 consecutive patients receiving first-line pembrolizumab with chemotherapy (n=70) or as monotherapy (n=15). Maximum and mean standardized uptake value, metabolic tumor volume (MTV), total lesion glycolysis and bone marrow-/ spleen to liver ratio (BLR/SLR) were calculated. Kaplan-Meier analyses and Cox-regression models were used to assess progression-free/overall survival (PFS/OS) and their determinant

variables.

Multivariate selection for PFS/OS revealed MTV as most relevant PET/CT biomarker ($p < 0.001$). Median PFS/OS were significantly longer in patients with $MTV \leq 70$ mL versus > 70 mL (PFS: 10 months (M; 95% confidence interval 4-16) vs. 4M (3-5), $p = 0.001$; OS: not reached vs. 10M (5-15), $p = 0.004$). Disease control rate was 81% vs. 53% for $MTV \leq / > 70$ mL ($p = 0.007$). BLR ≤ 1.06 versus > 1.06 was associated with better outcomes (PFS: 8M (4-13) vs. 4M (3-6), $p = 0.034$; OS: 19M (12-/-) vs. 6M (4-12), $p = 0.005$). In patients with $MTV > 70$ mL, concomitant BLR ≤ 1.06 indicated a better prognosis.

Higher MTV is associated with inferior PFS/OS in first-line ICI treated NSCLC, with BLR allowing additional risk stratification.

Key words

Total metabolic tumor volume, bone marrow to liver ratio, PET/CT, overall survival, immunotherapy, immune checkpoint inhibitor, standardized uptake value, response prediction

Introduction

Positron-emission tomography/computed tomography (PET/CT) enables functional visualization and quantification of malignant lesions in various cancer entities. In lung cancer, the application of PET/CT is recommended in staging of both limited and advanced disease.[1–4] In the last decade, immune-checkpoint inhibitors (ICI) directed against programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) brought major therapeutic advances especially in non-small cell lung cancer (NSCLC). Originally introduced as second-line therapy,[5–8] PD-1/PD-L1-blockade alone or as a combination therapy together with platinum-based doublet chemotherapy has moved into first-line therapy, leading to improved survival and response rates.[2,9–11] A considerable fraction of patients has shown a long-term benefit in follow-up,[12,13] although by far not all respond to such treatment.

The challenge of predicting favorable responses is still ongoing, whereas biomarkers like PD-L1 expression, tumor mutational burden or presence of targetable genetic tumor alterations are being widely applied.[14] Also, clinical or laboratory parameters like Eastern Cooperative Oncology Group (ECOG) performance status, neutrophil to lymphocyte ratio or lactate dehydrogenase have been suggested,[14,15] but each of them provides only limited predictive properties on the individual patient's level.

Several biomarkers derived from PET/CT imaging have been reported to predict outcomes in various malignancies treated with ICI.[4,16,17] Concerning NSCLC treated with chemotherapy or ICI, especially volume-based PET/CT variables like total (whole-body) metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been shown predictive properties in terms of therapy response and survival.[18–26] Of interest, the combination of the quantitative PET/CT biomarker MTV and the blood-based biomarker derived neutrophil to lymphocyte ratio (DNLR)

had predictive impact in NSCLC patients receiving ICI.[26–28] Similar to DNLR, also PET/CT allows an estimation of the activity of lymphatic tissues, as usually expressed by the bone marrow to liver ratio (BLR) or the spleen to liver ratio (SLR). In malignant melanoma, higher BLR as well as SLR have been reported to be associated with an unfavorable prognosis.[29,30] Although bone marrow hypermetabolism is a known prognostic factor in resected or chemo(-radio)therapy treated NSCLC,[31–33] implications for ICI therapy of advanced NSCLC have not yet been reported.

Importantly, with some exceptions,[21,24,25] most existing evidence for quantitative PET/CT biomarkers in the context of ICI therapy is based on mono-immunotherapy cohorts in higher therapy lines, reflecting the initial regulatory approvals for nivolumab, pembrolizumab and atezolizumab.[5–8] However, first-line ICI therapy in combination with chemotherapy or as monotherapy for tumors with PD-L1 expression $\geq 50\%$ is currently regarded standard of care.[1,2,10,11,34,35] Whether the existing data on quantitative PET/CT biomarkers can be transferred to the present therapeutic setting is thus questionable, especially due to the increased application of chemotherapy together with ICI.

Consequently, it was our aim to evaluate the clinical implications of quantitative biomarkers derived from pre-therapy ^{18}F -FDG-PET/CT in a well-characterized retrospective cohort of patients receiving first-line ICI therapy with pembrolizumab in combination with chemotherapy or as monotherapy.

Materials and Methods

Patients:

Eighty-five consecutive patients who had undergone ^{18}F -FDG-PET/CT before receiving first-line ICI therapy with pembrolizumab between June 2018 and December 2019 were retrospectively identified, follow-up was accomplished until December 2020. The patient cohort was derived from the institutional NSCLC immunotherapy registry of Kepler University Hospital Linz. The patient registry as well as the present evaluation have been approved by the ethics committees of the federal state of Upper-Austria (EK Nr. 1139/2019), the need for patients' written informed consent was waived. All investigators had full access to the dataset used for this analysis. This study was conducted according to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.[36]

According to institutional standards, patients with PD-L1 expression <50% received a chemo-ICI combination with pembrolizumab and carboplatin/pemetrexed for non-squamous and carboplatin/paclitaxel for squamous histology.[10,11] Chemotherapy was given for four cycles with no further maintenance therapy, pembrolizumab was continued until progression or toxicity. Patients with PD-L1 expression \geq 50% could either receive pembrolizumab monotherapy or a combination with platinum-based doublet chemotherapy.[35] Patients were retrospectively followed from first-line ICI therapy initiation on to death or censored at the date of last verified contact. Disease progression and survival were retrospectively assessed by reviewing the relevant medical records, especially imaging studies and death certificates. First-line therapy was defined as first systemic treatment in stage IV or not otherwise treatable stage III disease, whereas previous therapies in potentially curable stages were not

considered. We excluded patients in clinical trials, on ICI/ICI combination therapies and patients, who had previously received ICI for NSCLC or other malignancies.

Image Acquisition Protocol and Analysis:

PET/CT imaging was accomplished in the staging process usually two to four weeks before therapy initiation, however a time span of a maximum of three months was allowed for inclusion if no tumor-specific therapy had been applied in that time.

PET/CT scans were performed using a dedicated Siemens Biograph 40 Truepoint PET/CT scanner (Siemens Medical Solutions, Illinois). Patients were kept fasting for at least six hours and blood glucose levels were measured before the injection of ^{18}F -FDG imaging to ensure that values were below 150 mg/dL. ^{18}F -FDG was administered at a dose of 3.7 MBq/kg through a peripheral vein sixty minutes prior to imaging. Sequential overlapping emission scans of the neck, chest, abdomen, and pelvis were acquired. PET imaging was performed in 3D mode at three minutes per bed position, using the same axial field as the CT scan. We performed image reconstruction using an ordered subset expectation maximization iterative reconstruction algorithm on a 128x128-pixel matrix (AW-OSEM, 2 iterations, 8 subsets), followed by post-reconstruction filtering using a Gaussian filter applied at 5.0mm Full Width at Half Maximum. All patients had attenuation-corrected images without intravenous contrast agent application. All PET/CT studies were reviewed by two specialist nuclear medicine physicians, who were blinded to the clinical data. For further analysis of quantitative PET/CT biomarkers, imaging data were transferred to a Hermes Workstation (Hermes Medical Solutions, Stockholm, Sweden).

Semiquantitative analysis of ^{18}F -FDG tumor uptake was performed with the Affinity Software Tool®. In this research, all SUV values were based on body weight. To determine the SUVmax, irregular isocontour regions of interest were drawn over

abnormal findings at 50% of maximum pixel value within the lesion. The volumes of all segmented individual lesions were summed to obtain the whole-body MTV for each patient.[37] TLG was calculated as the product of the MTV and the SUV_{mean} within the MTV.[38] BLR and SLR were calculated as the ratio of bone marrow/spleen and liver SUV_{max}. Bone marrow SUV_{max} was measured in the vertebral bodies of L1-L5, whereas areas with vertebral fractures and tumors/metastases were omitted. Spleen and liver SUV_{max} were calculated in a spherical VOI of three cm in the respective organ in an area with physiological morphology in the CT images, excluding e.g., metastases.

Laboratory Analyses:

C-reactive protein (CRP) and LDH were assessed using a Cobas® 8000 modular analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland), lymphocyte count was analyzed using a Sysmex® XN-3000 hematology analyzer (Sysmex Europe GmbH, Norderstedt, Germany). Expression of PD-L1 on tumor cells was determined using a 22C3 assay for Autostainer Link 48 by Dako (Agilent Technologies, Santa Clara, CA), a negative PD-L1 status was defined as membranous staining on <1% of viable tumor cells.

Response Assessment:

Radiological response to ICI therapy was routinely assessed every six to nine weeks by a CT scan of the chest and the upper abdomen using iodinated contrast medium unless contraindicated. Re-staging could be preponed due to suspected disease progression and additional imaging modalities like cerebral magnetic resonance tomography could be conducted according to the treating clinician's judgement. Response was graded according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[39] Disease control rate (DCR) was defined as patients with

complete/partial remission (CR/PR) or stable disease (SD) versus those with progressive disease (PD). Patients, who had died before the first scheduled CT re-staging (n=11) were counted as PD.

Statistics:

Statistical analyses were performed using R (R: A Language and Environment for Statistical Computing; Version 3.6.0; <https://www.R-project.org>). Progression-free and overall survival (PFS, OS) for all patients and in specified subgroups were evaluated using Kaplan-Meier-analyses, results were expressed as median in months (M) with 95% confidence interval (CI). The Kaplan-Meier curves were statistically compared using the log rank test, whereas a p-value<0.05 was regarded statistically significant. Uni- and multivariate models for PFS and OS were accomplished using Cox-regression analyses. For MTV and BLR, cut-off values for PFS and OS were calculated using graphical analysis in quartiles and maximally selected rank (MSR) statistics. Clinical variables included in the multivariate models were age (</≥70 years), sex, smoking history (</≥5 pack years), histological subtype (adeno-, squamous-cell carcinoma), ECOG (0,1/≥2), CRP (</≥0.5mg/dL), LDH (</≥250U/L), lymphocyte count (</≥1G/L), and PD-L1 expression (positive/negative).

Results

Quantitative PET/CT biomarkers were available in all 85 patients, patient disposition and baseline characteristics are presented in figure 1 and table 1. At the time of analysis, 68 subjects had shown tumor progression, while 53 had died, resulting in a PFS of 5M (4-8) and an OS of 14M (7-18). The median timespan from baseline PET/CT acquisition to ICI therapy initiation was 23 (interquartile range (IQR) 23) days, and 401 (IQR 441) days to the end of observation.

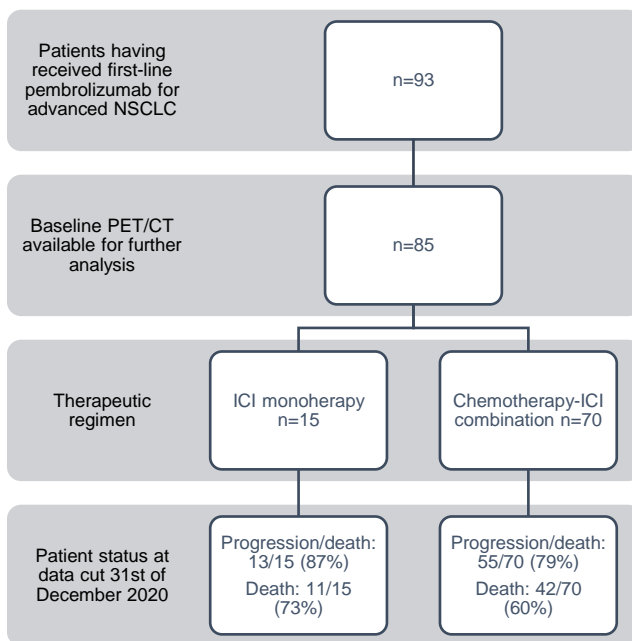


Figure 1. Patient disposition. NSCLC=non-small cell lung cancer, PET/CT=positron-emission tomography/computed tomography, ICI=immune checkpoint inhibitor

Patient Characteristics	
Median age (range; years)	64 (38-81)
Male sex (n, %)	56 (66)
ECOG (n, %)	
0	42 (49)
1	27 (32)
2+	16 (19)
Presence of brain metastases (n, %)	32 (37.6)
Smoking history ≥ 5 pack years (n, %)	79 (89.4)
Pack years (mean, SD)	44.5 (24.3)
Therapy Characteristics	
ICI monotherapy (n, %)	15 (17.6)
Median number of mono-ICI cycles (IQR)	3 (2.5)
Chemotherapy-ICI combination (n, %)	70 (82.4)
Median number of chemotherapy-ICI cycles (IQR)	4 (2)
Median number of mono-ICI maintenance cycles (IQR)	2.5 (8)
Tumor Characteristics	
Histological subtype (n, %)	
Adenocarcinoma	62 (73)
Squamous-cell carcinoma	22 (27)
NSCLC not otherwise specified	1 (1)
Positive PD-L1-status (n, %)	49 (58)
PD-L1 expression (n, %)	
not available	5 (6)
<1%	31 (36)
1-49%	20 (24)
$\geq 50\%$	29 (34)
Blood Biomarkers (mean, SD)	
C-reactive protein (mg/dL)	3.2 (5.3)
Lactate dehydrogenase (U/L)	331.2 (612)
Lymphocyte count (G/L)	1.3 (0.78)
PET/CT Biomarkers (mean, SD)	
SUVmax	16 (6.7)
SUVmean	7 (1.8)
Total metabolic tumor volume (mL)	121.6 (145.9)
Total lesion glycolysis	888.6 (1184.3)
Bone marrow to liver ratio	1.04 (0.27)
Spleen to liver ratio	0.81 (0.12)

Table 1. Baseline characteristics. ECOG=Eastern Cooperative Oncology Group, SD=standard deviation, ICI=immune checkpoint inhibitor, IQR=interquartile range, NSCLC=non-small cell lung cancer, PD-L1=programmed death-ligand 1, PET/CT=

positron-emission tomography/computed tomography, SUV=standardized uptake value

Using a Cox-regression model including all quantitative PET/CT biomarkers, univariate analyses for PFS showed significance for MTV ($p<0.001$), TLG ($p=0.002$) and BLR ($p=0.046$), while stepwise multivariate selection revealed only MTV ($p<0.001$) as significant. Similarly for OS, univariate analyses indicated significant interactions for MTV ($p=0.001$), TLG ($p=0.003$) and BLR ($p=0.003$), while multivariate selection again showed significance only for MTV ($p<0.001$). Due to these results, MTV and BLR were defined as respective tumor- and immunologically related quantitative PET/CT biomarker for subsequent analyses. Using graphical analysis of quartiles and MSR calculation, the optimum cut-off values for MTV and BLR regarding PFS were determined at value of 70mL and 1.06, respectively.

PFS and OS differed significantly according to the defined MTV and BLR subgroups as shown in table 2 and figure 2, whereas lower MTV and lower BLR were associated with a more favorable prognosis.

	Progression-free survival			Overall survival		
	Median	95% CI	p	median	95% CI	p
MTV\leq70mL	10	4-16	0.001	Not reached	7-/-	0.004
MTV$>$70mL	4	3-5		10	5-15	
BLR\leq1.06	8	4-13	0.034	19	12-/-	0.005
BLR$>$1.06	4	3-6		6	4-12	

Table 2. Median progression-free and overall survival according to MTV and BLR cutoff values. CI=confidence interval, MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

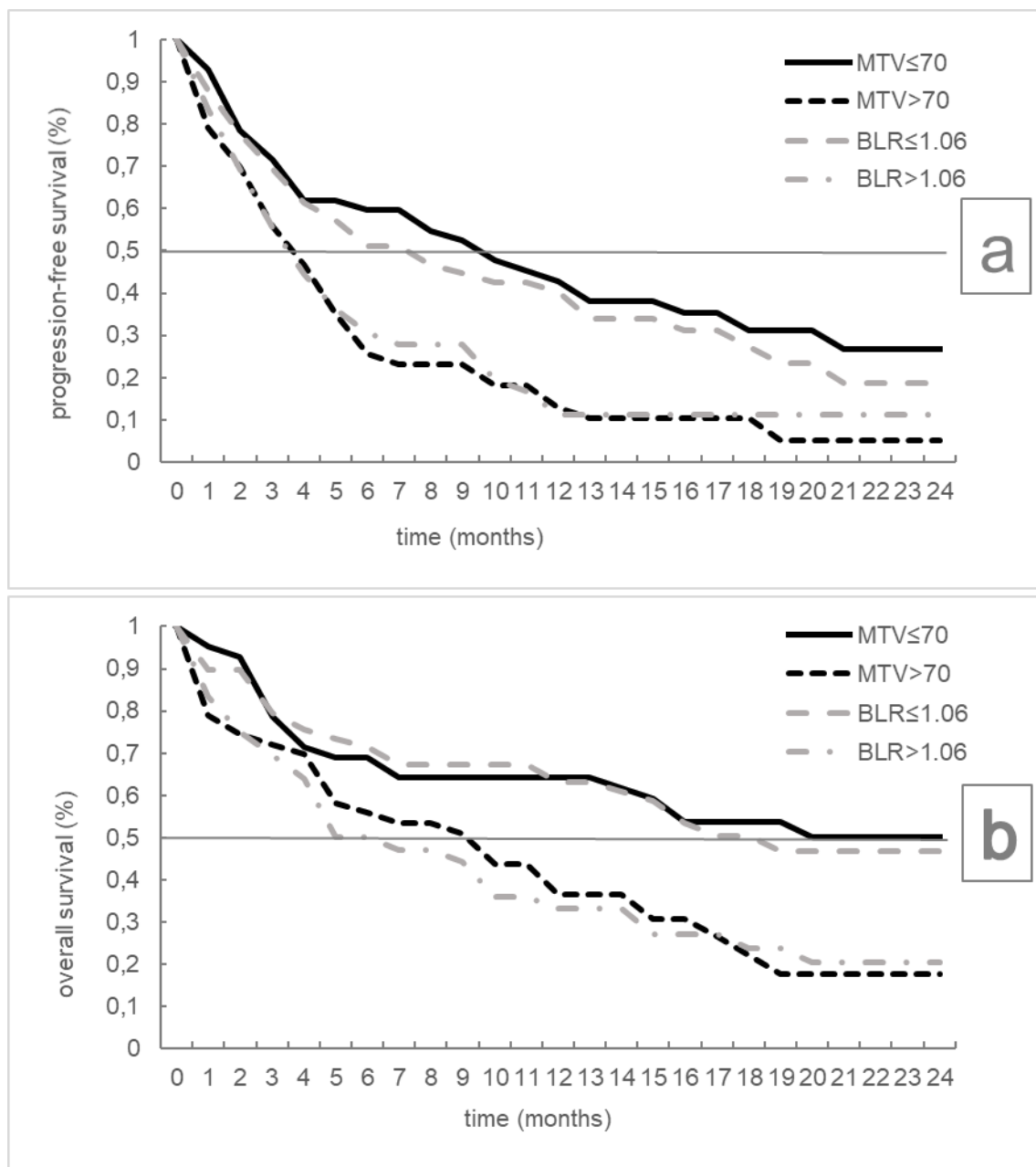


Figure 2. Kaplan-Meier curves for progression-free (a) and overall survival (b) according to MTV and BLR subgroups. MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

Best radiological response according to RECIST for MTV and BLR subgroups is visualized in table 3. Response rates differed significantly between patients with MTV ≤/ > 70 mL; DCR was 81% for MTV ≤ 70 mL vs. 53% for MTV > 70 mL ($p=0.007$).

	RECIST best response	Disease control rate
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	cut-off	n	CR, PR	SD	PD	p	CR, PR, SD	p
MTV	≤70mL	42	22 (52)	12 (29)	8 (19)	0.026	34 (81)	0.007
	>70mL	43	14 (33)	9 (21)	20 (46)		23 (53)	
BLR	≤1.06	49	23 (47)	12 (24)	14 (29)	0.536	35 (71)	0.317
	>1.06	36	13 (36)	9 (25)	14 (39)		22 (61)	

Table 3. Radiological best response and disease control rate according to RECIST.

RECIST=Response Evaluation Criteria in Solid Tumors, CR=complete remission, PR=partial remission, SD=stable disease, PD=progressive disease, MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

In an exploratory approach, we estimated the predictive power of MTV and BLR in the context of other, more established, patient- and tumor related prognostic biomarkers in uni- and multivariate regression models for PFS and OS. As shown in table 4, univariate analyses for PFS indicated a significant interaction for $LDH \geq 250U/L$, presence of brain metastases and $MTV > 70mL$, while the multivariate model showed significance only for MTV. Concerning OS, univariate analyses revealed an ECOG performance status ≥ 2 , $LDH > 250U/L$, $MTV > 70mL$ and $BLR > 1.06$ as significant, while ICI-monotherapy, $LDH \geq 250U/L$, PD-L1 positivity and $BLR > 1.06$ had significant implications on the multivariate model.

	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
	Progression-free survival				Overall survival			
ICI-monotherapy vs. chemotherapy-ICI combination	1.33 (0.70-0.52)	0.378			1.50 (0.74-3.04)	0.258	4.01 (1.63-9.87)	0.003
sex (male vs. female)	1.13 (0.66-1.95)	0.654			1.01 (0.55-1.84)	0.985		
age (>70 vs. ≤70 years)	1.18 (0.67-2.07)	0.567			1.16 (0.60-2.23)	0.666		
ECOG (2+ vs. 0,1)	1.64 (0.88-3.03)	0.117			2.20 (1.11-4.38)	0.025		
histology (squamous-cell vs. adenocarcinoma)	1.25 (0.69-2.24)	0.464			1.53 (0.80-2.93)	0.199		
>5 packyears (yes vs. no)	0.55 (0.24-1.30)	0.174			0.62 (0.25-1.57)	0.315		
LDH (>250 vs. ≤250U/L)	1.80 (1.05-3.07)	0.032			2.22 (1.23-4.00)	0.008	4.34 (2.02-9.33)	<0.001
CRP (>0.5 vs. ≤0.5mg/dL)	1.27 (0.64-2.51)	0.492			1.52 (0.68-3.40)	0.306		
PD-L1 (pos. vs. neg)	1.22 (0.73-2.05)	0.457			1.29 (0.72-2.31)	0.384	3.55 (1.54-8.14)	0.026
Lymphocyte count (>1 vs. ≤1G/L)	1.16 (0.68-1.98)	0.578			1.03 (0.57-1.87)	0.914		
Presence of brain metastases (yes vs. no)	1.70 (1.02-2.84)	0.043			1.45 (0.85-2.59)	0.170		
MTV (>70 vs. ≤70mL)	1.90 (1.12-3.23)	0.017	1.90 (1.12-3.23)	0.015	1.88 (1.03-3.42)	0.040		
BLR (>1.06 vs. ≤1.06)	1.63 (0.98-2.72)	0.061			2.10 (1.18-3.74)	0.012	2.09 (1.16-3.75)	0.014

Table 4. Uni- and multivariate analyses for progression-free and overall survival in all patients (n=85). HR=hazard ratio, CI=confidence interval, ICI=immune checkpoint inhibitor, ECOG=Eastern Cooperative Oncology Group, SD=standard deviation, IQR=interquartile range, NSCLC=non-small cell lung cancer, LDH=lactate dehydrogenase, CRP=C-reactive protein, PD-L1=programmed death-ligand 1, MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

To identify clinically relevant patient collectives defined by quantitative PET/CT biomarkers, four subgroups with MTV≤/ >70mL and BLR ≤/ >1.06 were analyzed for PFS and OS, respectively. As shown in table 5 and figure 3, the subgroup with MTV>70mL and BLR>1.06 had considerably reduced PFS/OS, while patients with MTV>70mL showed a prognostic benefit in if their BLR concomitantly was ≤1.06.

	n	Progression-free survival			Overall survival		
		median	95% CI	p	median	95% CI	p
MTV≤70mL + BLR≤1.06	31	9	4-18	<0.001	Not reached	7-/-	<0.001
MTV≤70mL + BLR>1.06	11	11	2-/-		Not reached	3-/-	
MTV>70mL + BLR≤1.06	18	5.5	3-13		17	6-/-	
MTV>70mL + BLR>1.06	25	3	2-5		5	2-10	

Table 5. Median progression-free and overall survival according to combined MTV and BLR subgroups values. CI=confidence interval, MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

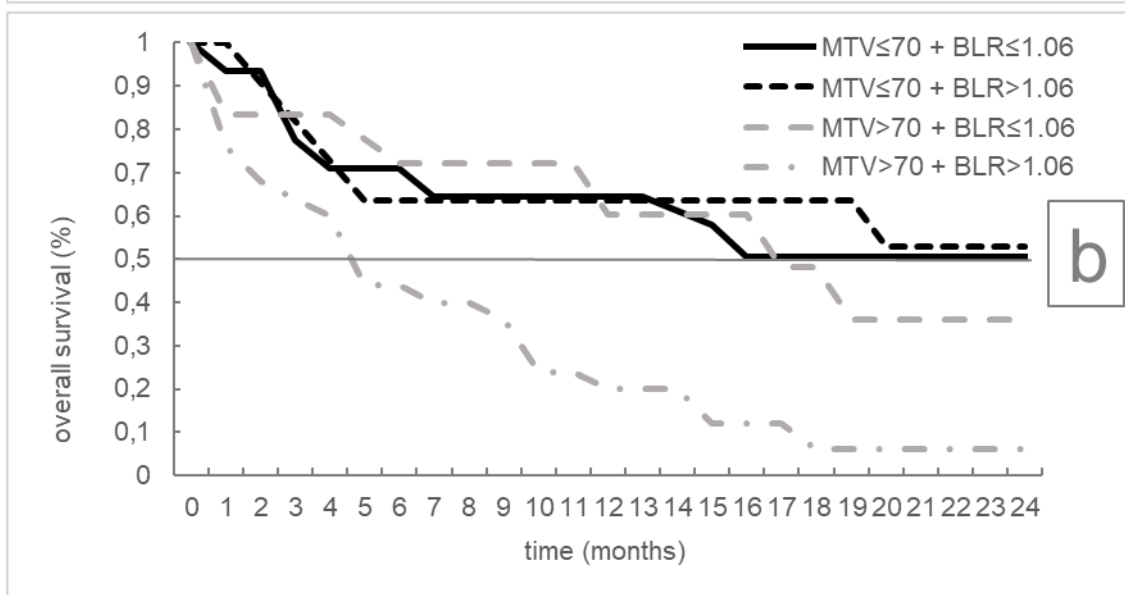
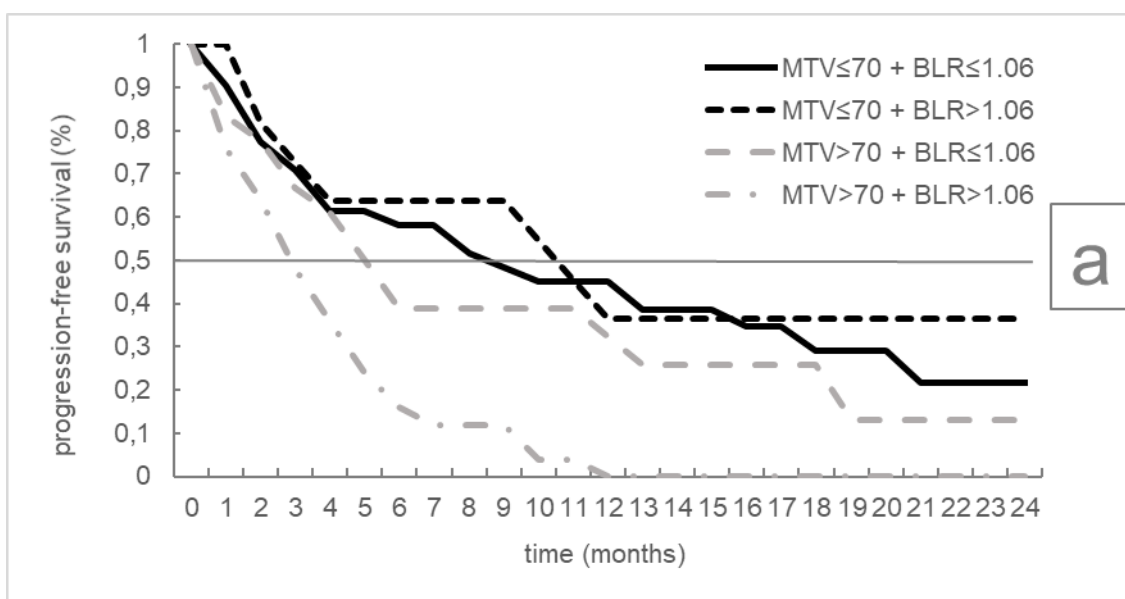


Figure 3. Kaplan-Meier curves for progression-free (a) and overall survival (b) according to combined MTV and BLR subgroups. MTV=metabolic tumor volume, BLR=bone marrow to liver ratio

In a subgroup analysis among patients with PD-L1 \geq 50% (n=29), individuals having received ICI-monotherapy had inferior PFS and OS as compared to chemotherapy-ICI combination, regardless of MTV. For MTV \leq 70mL, median PFS and OS were not reached in the chemo-ICI group and 4M (1-6) and 14M (1-/) in the mono-ICI group, respectively. Patients with MTV $>$ 70mL had a median PFS and OS of 3M (2-10) and 6M (3-18) with chemo-ICI and 2.5M (1-7) and 3M (1-/) with mono-ICI.

Discussion

Our analyses indicate that among the quantitative PET/CT variables evaluated, MTV was the most relevant tumor-related predictive biomarker in first-line ICI-treated NSCLC. Patients with lower $MTV \leq 70\text{mL}$ had not only significantly longer PFS and OS, but also a significantly higher radiological response and disease control rate as compared to patients with a higher metabolic tumor burden. Additionally, bone marrow metabolism as assessed by BLR may have the potential to differentiate between favorable and adverse prognosis especially in those patients with higher MTV. In uni- and multivariate analyses for PFS and OS, both MTV and BLR showed hazard ratios comparable to traditional prognostic factors like ECOG performance status or the presence of brain metastases.

From a clinical point of view, it is not surprising that metabolically active tumor burden as measured by MTV turned out as the most relevant tumor-related quantitative PET/CT biomarker in our cohort. Similar observations have been reported for various disease stages of NSCLC, using PET/CT or conventional CT imaging for both the determination of baseline tumor burden and response to ICI.[20,22,27,40,41]

Concerning first-line treatment using mono-ICI therapy, Dall'Olio et al. recently reported an $MTV \geq 75\text{cm}^3$ as a biomarker of poor prognosis in a cohort of 34 pembrolizumab-treated NSCLC patients with PD-L1 expression $\geq 50\%$, with an OS of 4.7M (0.3-9.1), while median OS was not reached in patients with $MTV < 75\text{m}^3$. [21]

These results are similar to our findings with a MTV threshold calculated at 70mL, but with a better OS of 10M (5-15) in our reported $MTV > 70\text{mL}$ group, which may be due to the addition of chemotherapy in the majority of patients. Seban et al. evaluated a cohort of 63 patients in the same therapeutic setting and identified $MTV > 84\text{cm}^3$ and $SUV_{\text{mean}} > 10.1$ as significant predictors of long-term benefit, PFS and OS. [24]

Similarly, Yamaguchi et al. reported on 48 patients treated with first-line pembrolizumab for NSCLC with PD-L1 \geq 50% and identified MTV as significant uni- and multivariate prognostic determinant.[25] In a cohort with 42 out of 57 NSCLC patients being treated with first-line ICI, Polverari et al. found associations of higher MTV and TLG with radiological disease progression.[23] All these studies consistently show very similar findings as reported in our cohort, especially concerning the major prognostic implications of MTV. However, in our patient collective, the vast majority received chemo-ICI combination treatment, which reflects the current clinical practice in a considerably larger patient population as compared to the discussed evaluations of mono-ICI in NSCLC with PD-L1 \geq 50%. Our findings regarding BLR could have additional impact on patient management, since lower BLR may identify patients with a better treatment response despite higher tumor burden. This resembles previous reports in cohorts of NSCLC and cutaneous melanoma patients, where the combination of MTV with DLNR,[27,28] TLG with DLNR,[26] as well as of MTV with BLR[29] provided similar prognostic information.

Reviewing these results, the question arises, how such biomarker information derived from PET/CT could benefit clinical decision-making on the individual patient's level. Currently, for NSCLC patients with higher baseline MTV and BLR and without specific molecular targets, alternative first-line treatment options next to mono-ICI or chemo-ICI are not available. Still, our findings have several implications on daily clinical practice: First, we suggest that PET/CT should be performed at baseline in all advanced NSCLC patients receiving ICI treatment. Given the current scarcity of predictive biomarkers in these patients, our results and previous evaluations clearly suggest that biomarkers derived from PET/CT have prognostic relevance. Second, in line with other authors,[21] we propose that patients with high tumor burden as

depicted by MTV should receive chemo-ICI combination rather than mono-ICI therapy. Also, concomitant radiotherapy of the primary tumor or of metastatic lesions could further enhance outcomes in such cases.[42,43] Third, patients at risk for early progression as identified by our reported PET/CT-derived biomarkers should be monitored more closely during initial therapy. Treating clinicians should timely ensure the availability of a complete panel of currently targetable genetic tumor alterations needed for second-line treatment decisions, such as the presence of a KRAS p.G12C mutation.[44] Such patients could also benefit from participation in clinical trials on substances aiming at enhancing the anti-cancer activity of existing (chemo-)immunotherapy agents, e.g. Canakinumab or Tiragolumab.[45,46] Also, novel molecular imaging tracers and “theranostic” substances currently under development for different tumor entities could provide new incentives in that field.[4,47–51]

Our reported analysis has inherent limitations, but also strengths that should be addressed: The limited sample size and the retrospective study design warrant further larger-scale and prospective trials in that field. Still, it is the largest cohort of first-line mono- and chemo-ICI-treated NSCLC patients for PET/CT biomarker analyses we are aware of. This allows an insight into a patient collective of high clinical relevance, reflecting the current challenges better than previously reported analyses of ICI monotherapy cohorts in second- or higher therapy line or first-line patients with PD-L1 \geq 50%. Another limitation is the single-center study design and the current lack of standardized methods for evaluation of quantitative PET/CT biomarkers, although we sought to use similar approaches as suggested by previous studies. Bone marrow hypermetabolism has been repeatedly reported as prognostic factor;[29–33] however, its exact pathophysiological correlate is unclear. Although we sought to exclude metastatic or traumatic lesions within the region of interest in the

lumbar vertebral bodies, diffuse metastatic bone marrow infiltration cannot be ruled out, as bone marrow biopsies are usually not assessed in stage IV NSCLC patients due to the lack of clinical consequences.

Conclusions

Quantitative baseline PET/CT biomarkers in ICI-treated advanced NSCLC patients can provide essential predictive biomarker information, both concerning metabolic tumor characteristics, but also reflecting the immune system. The combination of high MTV and BLR identifies a clinically highly relevant group of patients with a poor prognosis that warrants intensified diagnostic and therapeutic efforts by the clinician as well as future research activity concerning additional treatment options.

Author Contributions: All authors have made significant contributions to this manuscript and meet the criteria for authorship as established by the International Committee of Medical Journal Editors, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding: This research received no external funding.

Institutional Review Board Statement: The patient registry as well as the present evaluation have been approved by the ethics committees of the federal state of Upper-Austria (EK Nr. 1139/2019).

Informed Consent Statement: The need for patients' written informed consent was waived according to the institutional ethics committee's regulations for non-interventional retrospective studies.

Data Availability Statement: As mandated by the Ethics Committee of Upper Austria, publication or dissemination of any possibly identifiable patient data from the present registry is prohibited. The dataset used for the present analyses contains very detailed and thus possibly identifiable patient data, so that a publication of the full database is not possible. However, upon reasonable request to the authors and if permitted by the Ethics Committee of Upper Austria in an amendment to the study protocol, anonymized data can under certain circumstances be shared.

Acknowledgements: None.

Conflicts of interest: The authors report no conflicts of interest.

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